TOXICOLOGY OF INHALED PLUTONIUM*†

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ABSTRACT

In a series of experiments over the past 14 years, several plutonium compounds were administered to experimental animals by inhalation to define the disposition of plutonium in the body and the resultant biological responses at the cellular and organ levels. All compounds showed a relatively long residence time in the lung. Plutonium translocated from the lung to other tissues accumulated principally in the tracheobronchial lymph nodes and to a lesser extent in liver, abdominal lymph nodes and bone. After several years, plutonium in the tracheobronchial lymph nodes of dogs comprised about 40% of the total PuO_2 initially deposited in the alveolar lung. The biological effects observed in these studies included lymphopenia, cellular changes in lung and tracheobronchial lymph nodes, respiratory insufficiency and pulmonary neoplasia, depending upon amount of plutonium inhaled.

INTRODUCTION

The importance of plutonium fuels in nuclear power programs is steadily increasing in many countries. As larger and larger quantities of plutonium are processed in laboratories and fuels fabrication plants, the chance of human contamination increases. Experience to date indicates that most human internal plutonium contamination cases occur as the result of inhaling air in which plutonium was accidentally dispersed. The next serious route for internal plutonium deposition is through contaminated wounds in the skin. This discussion, however, will be concerned only with the inhalation route of entry. During the course of research which has been in progress for 15 years, we have obtained extensive information about several important aspects of inhaled plutonium. While there is still much more to be known, we can use our animal data to begin to develop an understanding of the toxicology of inhaled plutonium. In this paper I will summarize our knowledge of the toxicology of inhaled plutonium obtained in a number of animal experiments. Most of these experiments have been reported extensively in the literature and were summarized in a recent document.[1]

## CELLULAR INTERACTION WITH PLUTONIUM

The response of a living cell to the presence of highly radioactive particles such as plutonium determines the disposition of the particle in the body and the subsequent biological effects. Plutonium particles deposited in the lung are rapidly taken up by macrophages[2] and by type I alveolar epithelial cells.[3] Figure 1 is an autoradiographic demonstration of the phagocytosis of plutonium particles by lung macrophages. At the top is an epon section of lung taken from a rat 7 days after inhalation of $^{239}PuO_2$. At the bottom is a macrophage from a cytosmear isolated from a saline wash of a rat lung. The alpha tracts arise principally from one part of the cell[2], i.e., from discrete lysosomal structures containing the PuO_2 particles.

Using electron microscopic autoradiography, it was possible to identify plutonium particles localized within macrophages.[4] This is illustrated in Figure 2. A large mass of plutonium is found in this cell. Tracks of reduced silver halide grains show the path of alpha particles emitted from the plutonium.

These observations demonstrated that plutonium particles may be rapidly engulfed by macrophages and epithelial cells and that the phagocytosis of plutonium particles is a mechanism by which plutonium can be concentrated into "hot spots" within a tissue, and localized in specific cell types in the lung.

A. Section of lung removed at 7 days after inhalation,
   fixed in glutaraldehyde and embedded in epon. Auto-
   radiogram, 14-day exposure, Richardson's Stain. Note
   alveolar macrophage in upper left-hand corner within
   an alveolus. 1300X
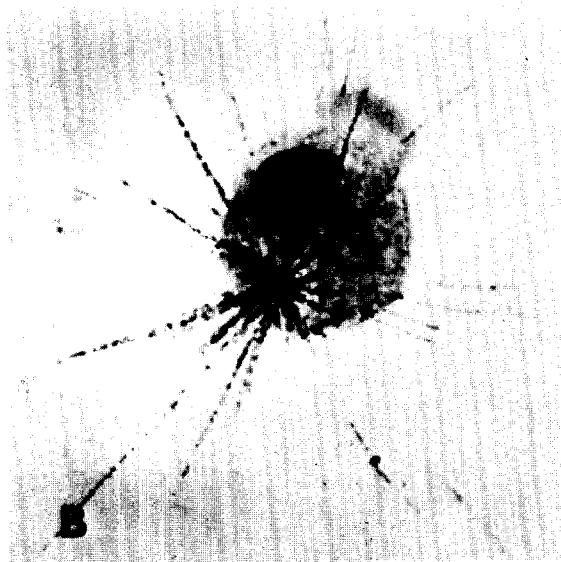
B. Cytosmear of pulmonary macrophage isolated from lung
   lavage at 1 hour after inhalation of particles. Auto-
   radiogram, 14-day exposure, Giemsa Stain. 1300X

FIGURE 1. Autoradiographic Demonstration of $^{239}PuO_2$ Particle
          Phagocytosis by Rat Lung Macrophage. A. Lung
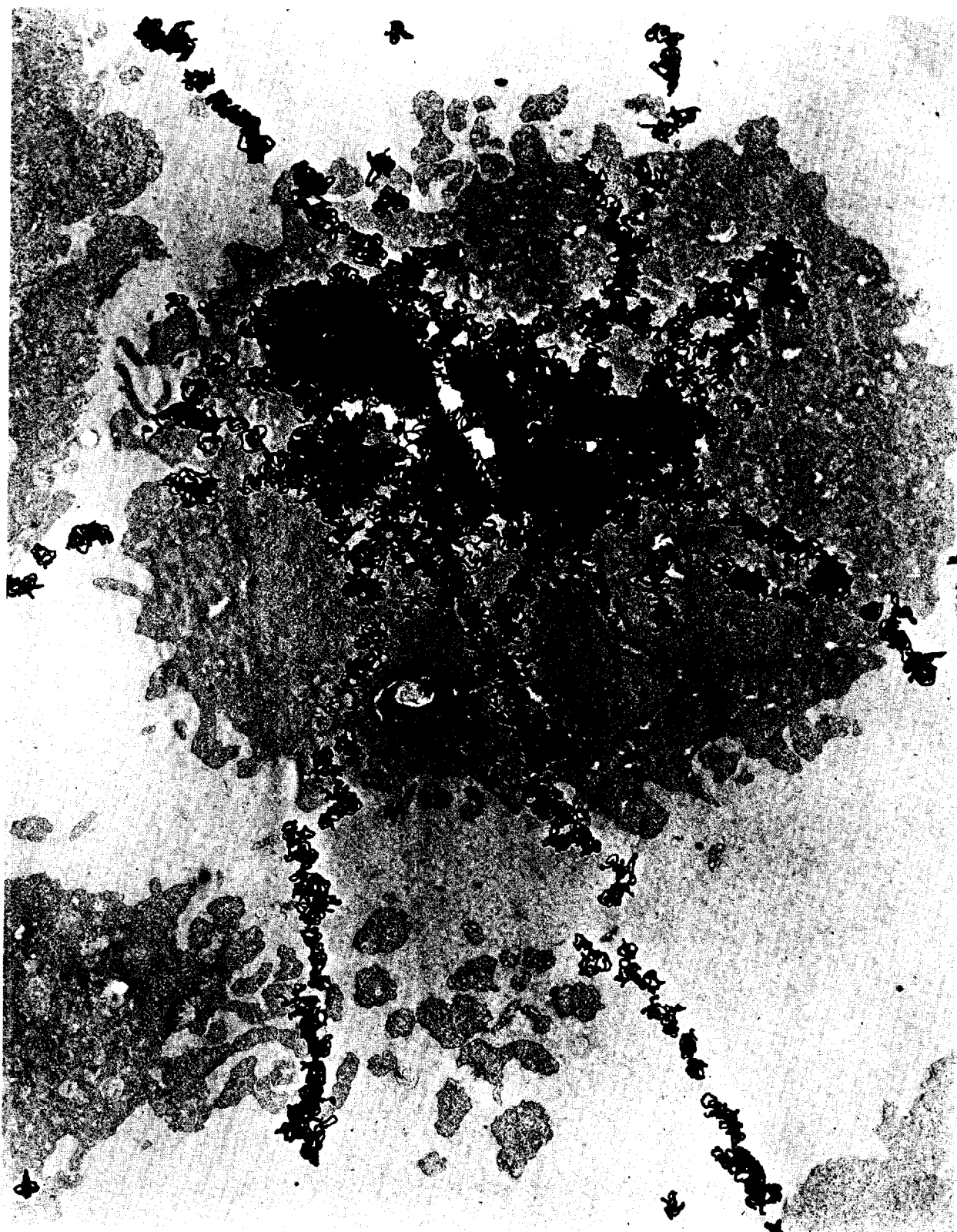   Section; B. Cytosmear from Lung Wash[2]

FIGURE 2.   Electromicrogram of an Autoradiogram of a Rat
            Macrophage Containing ^{239}Pu Particles (4)

DISPOSITION OF INHALED PLUTONIUM

Three plutonium compounds have been studied in more than 200 beagle dogs to determine the dynamics of plutonium retention, distribution, and excretion following inhalation. Some studies have been done with $Pu(NO_3)_4$ and PuF_4, but the major interest has been PuO_2, which seems to be the plutonium compound most likely to be encountered in an accident.
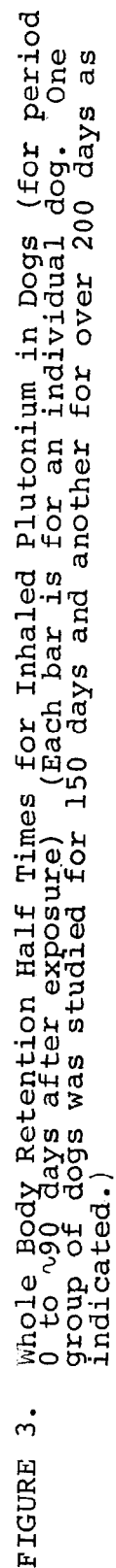
A. Whole Body Retention

Whole body retention half times are compared in Figure 3 for a number of different plutonium compounds.[1] Several oxides were studied which differed by the method in which they were prepared or differed in particle size. Data are also shown for PuF_4[5] and $Pu(NO_3)_4$.[6]
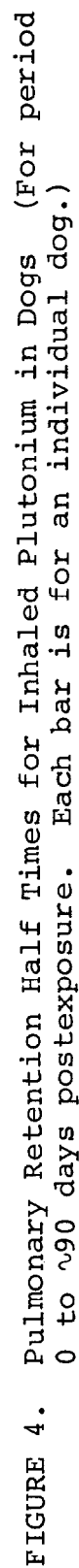
Maximum retention occurred in those animals which inhaled an oxide prepared by heating plutonium metal to 450° and the least retention occurred in those which inhaled PuF_4. Of the oxides, the 900° calcined oxalate with a particle size of 0.1 μm, MMD, was retained the least, similar to the nitrate. It can be seen that particle size was an important factor by comparing the retention of the small particle size 900° oxide with the 1000° oxide which had a particle size a factor of twenty larger. The larger particle size oxide showed greater whole body retention than the small sized PuO_2.

B. Pulmonary Retention

In Figure 4, the pulmonary retention half times are compared.[1] The oxides separate into two groups. Those showing the greatest pulmonary retention were the 1000° oxalate and the two oxides prepared from the metal. The half times ranged between 600 and 1000 days. Those showing the most rapid clearance were the two oxides with the smallest particle size of about 0.1 μm MMD, both calcined at relatively high temperatures. The third oxide in this group showing the lowest retention was the one prepared by calcining oxalate at a relatively low temperature, 350°; the particle size was a factor of 20 above those of the other two in this group. The half times ranged between 250 and 500 days. These agree with those reported by Morrow for dogs exposed to $^{239}PuO_2$ with a MMD of about 0.5 to 1.5 μm.[7] We conclude that both particle size and the process by which the oxide is formed influence its retention in the lung.

The pulmonary retention of PuF_4 was less than the oxide, but still somewhat greater than for the $Pu(NO_3)_4$.

FIGURE 3. Whole Body Retention Half Times for Inhaled Plutonium in Dogs (for period 0 to ~90 days after exposure) (Each bar is for an individual dog. One group of dogs was studied for 150 days and another for over 200 days as indicated.)

FIGURE 4. Pulmonary Retention Half Times for Inhaled Plutonium in Dogs (For period 0 to ~90 days postexposure. Each bar is for an individual dog.)

C. Disposition

Figure 5 shows the comparative disposition of the plutonium oxides.[1] The data are expressed as percent of alveolar deposited plutonium. Several points are obvious: (1) The oxalate calcined at 350° showed the greatest accumulation in the tracheobronchial lymph nodes. (2) The 750° $^{238}PuO_2$, with a particle size of 0.1 µm MMD, showed the greatest translocation to other tissues. (3) The 900° $^{239}PuO_2$, also with a particle size of 0.1 µm MMD, showed the greatest excretion in the feces.

Figure 6 shows the relative disposition of PuF_4 and $Pu(NO_3)_4$.[1] In view of the relative high translocation of the $Pu(NO_3)_4$ to other tissues, it is surprising that the amount excreted in urine was so small. Urinary excretion was not much greater than that which occurred after inhalation of the oxide. Of all the plutonium compounds studied, urinary excretion of plutonium was greatest after inhalation of PuF_4. Translocation of plutonium was considerably less after inhalation of PuF_4 than after inhalation of $Pu(NO_3)_4$, possibly because more was excreted in urine. Translocation was also less than for $^{238}PuO_2$ with a small particle size of 0.1 µm, MMD. It should be noted that in both the $Pu(NO_3)_4$ and the $^{238}PuO_2$ experiments, considerable pathology occurred due to the high doses. This may have altered the disposition of the plutonium.

The results obtained in this series of experiments clearly illustrate the important influence of chemical and physical properties of the inhaled plutonium aerosol on the disposition of the plutonium in the body. The findings are relevant to the potential biological effects which may occur after inhalation of plutonium and should be useful for interpretation of bioassay data.

LONG-TERM $^{239}PuO_2$ STUDIES

The most extensive studies have been with $^{239}PuO_2$ prepared by calcining the oxalate at a temperature of about 350°.[8] The particle size of this material was about 0.3 to 0.5 µm, CMD, and about 3 µm, MMD. From nearly 100 dogs, over a period of 10 years, we have accumulated extensive data on the disposition of this one particular plutonium dioxide. Data collected to date are summarized in Figure 7.[9] Time is expressed as hundreds of days. Therefore, the time period covers about 9 years postexposure. Retention of plutonium in the lung appears to be nearly exponential with time. A curve representing a 1000-day retention half time was drawn through the data.

$^{239}PuO_2$ ← → $^{238}PuO_2$

				900° OXALATE (150 DAYS)	
1000° OXALATE	350° OXALATE	450° METAL	123° METAL		750° OXALATE

μCi DEPOSITED IN ALVEOLI

| 1.9 | 30 | 7.7 | 20 | 1.2 | 92 47 |
| 3.4   6.5 | 6.4   20 | 1.1   5.2 | 1.5   7.5 | 2.3   1.4 | 90   61 |

Pu CONTENT, % OF ALVEOLAR-DEPOSITED Pu

100
90
80
70
60
50
40
30
20
10
0

LUNG
TRACHEOBRONCHIAL LYMPH NODES
ALL OTHER TISSUES
FECES
URINE

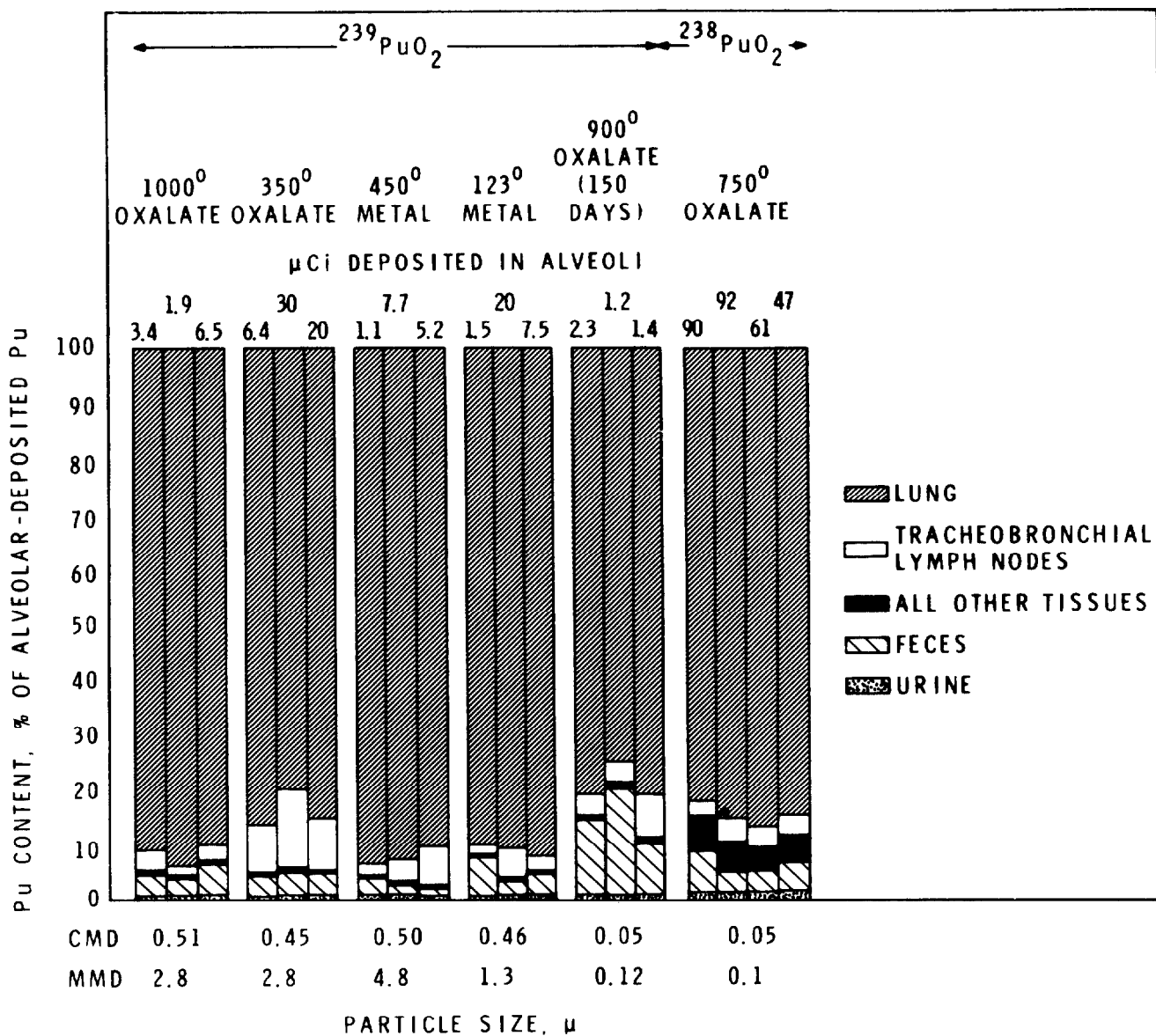| CMD | 0.51 | 0.45 | 0.50 | 0.46 | 0.05 | 0.05 |
| MMD | 2.8 | 2.8 | 4.8 | 1.3 | 0.12 | 0.1 |

PARTICLE SIZE, μ

FIGURE 5. Disposition of Inhaled PuO_2 in Dogs after 90 Days
(Each bar is for an individual dog. One group
was studied for 150 days as indicated.)

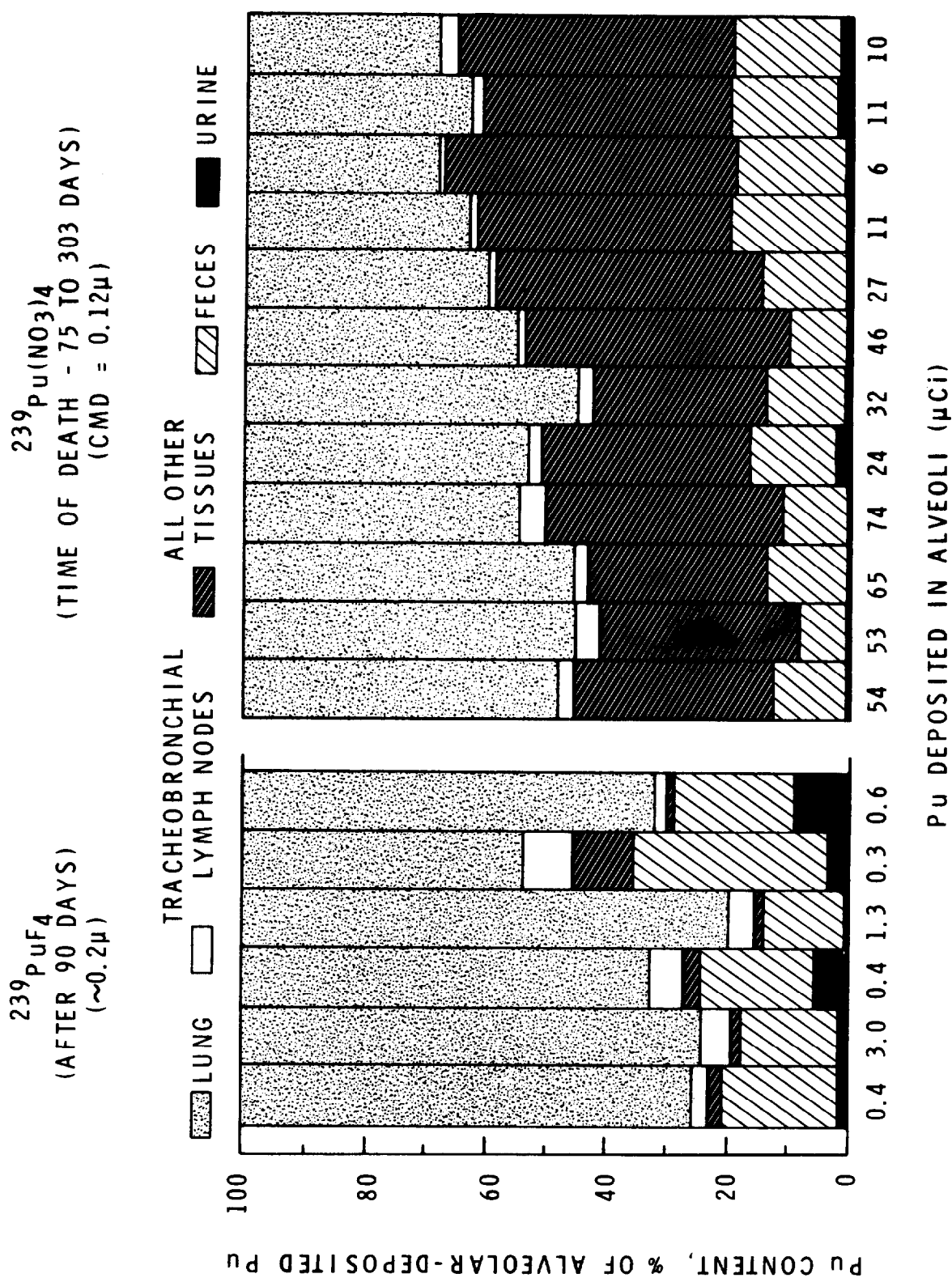FIGURE 6. Disposition of Inhaled PuF$_4$ and Pu(NO$_3$)$_4$ in Dogs (Each bar is for an individual dog. Of the dogs exposed to Pu(NO$_3$)$_4$, the first four from left to right were studied from 75 to 103 days after exposure; the next four, from 109 to 138 days; the next two, 172 and 199 days; and the last
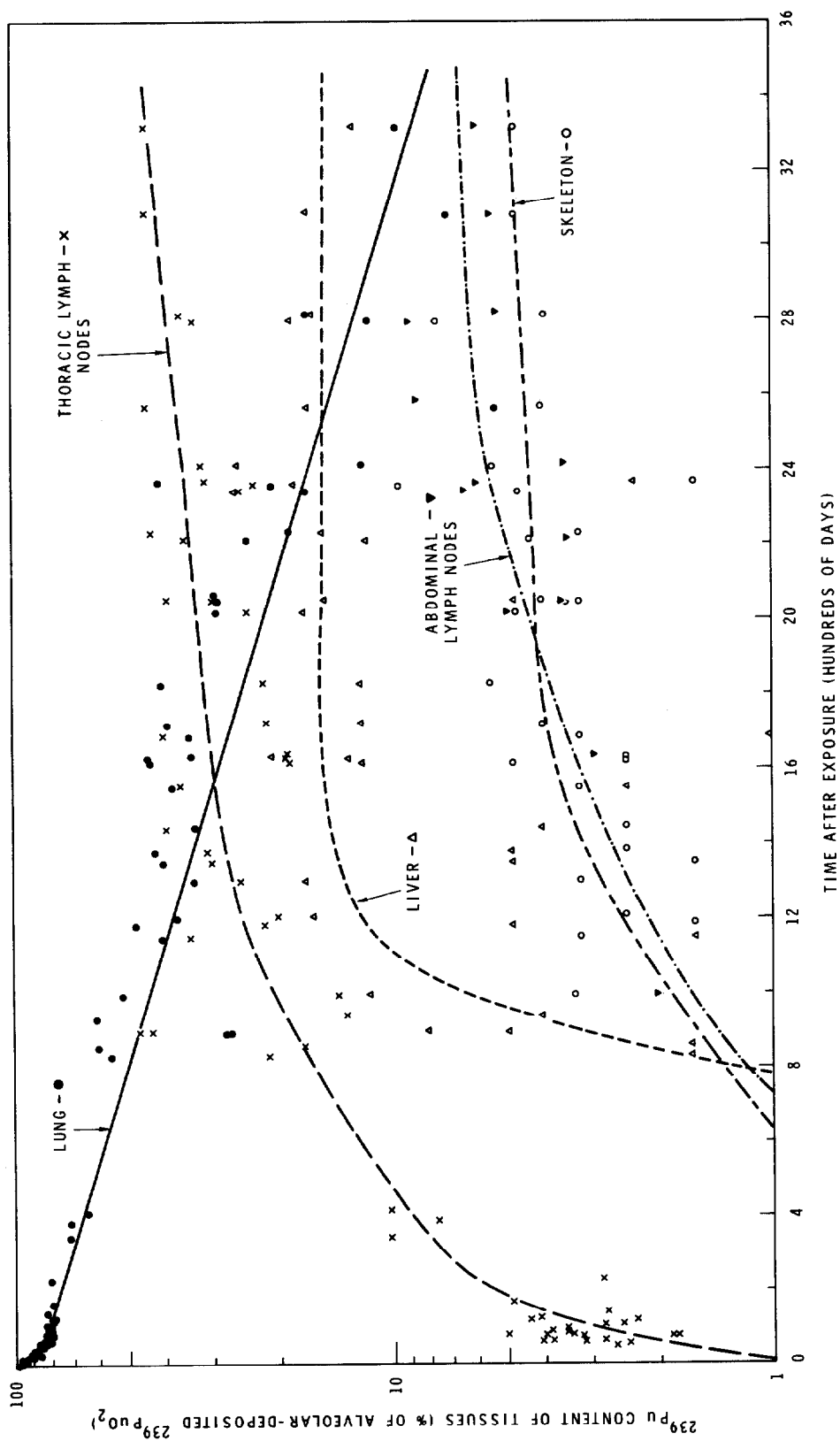
FIGURE 7. Retention and Translocation of Alveolar-Deposited $^{239}PuO_2$ in Dogs (CMD = $\sim$0.4 μm, MMD = $\sim$3 μm. Each set of values for the 5 tissues given is for an individual dog.)

The accumulation of plutonium in the tracheobronchial lymph nodes largely occurred early, within 3 years after exposure, but continued for several years. The tracheobronchial lymph nodes appear to accumulate at least 40% of the amount of plutonium initially deposited in the alveoli. This represents a major route for clearance of plutonium from lung. Significant accumulation of plutonium also occurred in the abdominal lymph nodes, including hepatic nodes, reaching levels as high as 8%. The immediate source of plutonium accumulating in these nodes is not known, but may include the liver. Accumulation of plutonium in liver was significant after about 2 years after exposure. The liver burden increased markedly to about 15-20% of alveolar deposition and remained at that level.

Translocation to the bone occurred more gradually, reaching 3 to 4% of the alveolar deposition after 4-5 years. Maximum values were nearly 5% in several dogs, but the skeleton of one dog had about 9.5% of the alveolar-deposited plutonium after about 6-1/2 years.

The relative concentration of plutonium in these tissues is of special interest because it indicates the relative radiation doses to the tissues. Examples of these values are shown in Table 1.[10] The average concentration of plutonium was 100 to 1000 times higher in the thoracic lymph nodes than in the lung 5 to 9 years after exposure. High concentrations of plutonium also occurred in lymph nodes from the abdominal cavity, especially the hepatic lymph nodes. The concentration of plutonium in the liver, spleen and bone was about an order of magnitude less than in lung.

PLUTONIUM TOXICITY

In our studies of inhaled plutonium we have looked for numerous clinical signs of biological injury. However, inhaled plutonium causes rather specific changes. The time of onset and extent of changes are dose dependent.

A. Hematology

The first indication of a pathologic change in animals which have inhaled PuO_2 is lymphopenia. This has been a consistent finding in all of our studies.[8,11,12] An example of this response is shown in Figure 8.[13]

The lymphocyte counts of dogs exposed to plutonium are compared with control values. Values are given for two different body burden levels of plutonium. Dogs with a body burden of 0.2 to 1.0 μCi showed lymphocyte counts appreciably less than those of the controls, which decreased with the age of the animals. There were no

TABLE 1.

Pu CONCENTRATION IN DOG TISSUES AFTER INHALATION OF ^{239}PuO$_2$

Dog Number	Survival (Months after Exposure)	Terminal Body Burden (μCi)	Plutonium Concentration (nCi per gram wet tissue)						
			Thoracic Lymph Nodes*	Abdominal Lymph Nodes	Lungs	Liver	Other Lymph Nodes***	Spleen	Skeleton
258	68	1.4	4400	30	5.2	1.1	0.6	0.4	0.06
281	74	1.7	2400	29	5.3	0.7	0.2	0.1	0.12
249	78	1.0	280	2	2.1	0.6	0.5	0.3	0.5
283	79	0.8	460	2	2.6	0.5	0.3	0.6	0.12
266	80	0.7	2400	5	1.2	0.6	1.0	0.7	0.06
273	85	1.4	3700	157**	1.1	1.1	0.6	0.3	0.11
278	93	0.8	1200	214**	1.2	0.5	0.1	0.4	0.11
254	94	0.6	2600	92**	1.5	0.4	0.2	0.2	0.03
1	103	0.6	1400	1	0.7	0.3	0.4	0.3	0.04
109	110	0.4	420	90**	0.7	0.3	0.1	0.1	0.04

*Tracheobronchial or Mediastinal Lymph Nodes

**Hepatic Lymph Nodes

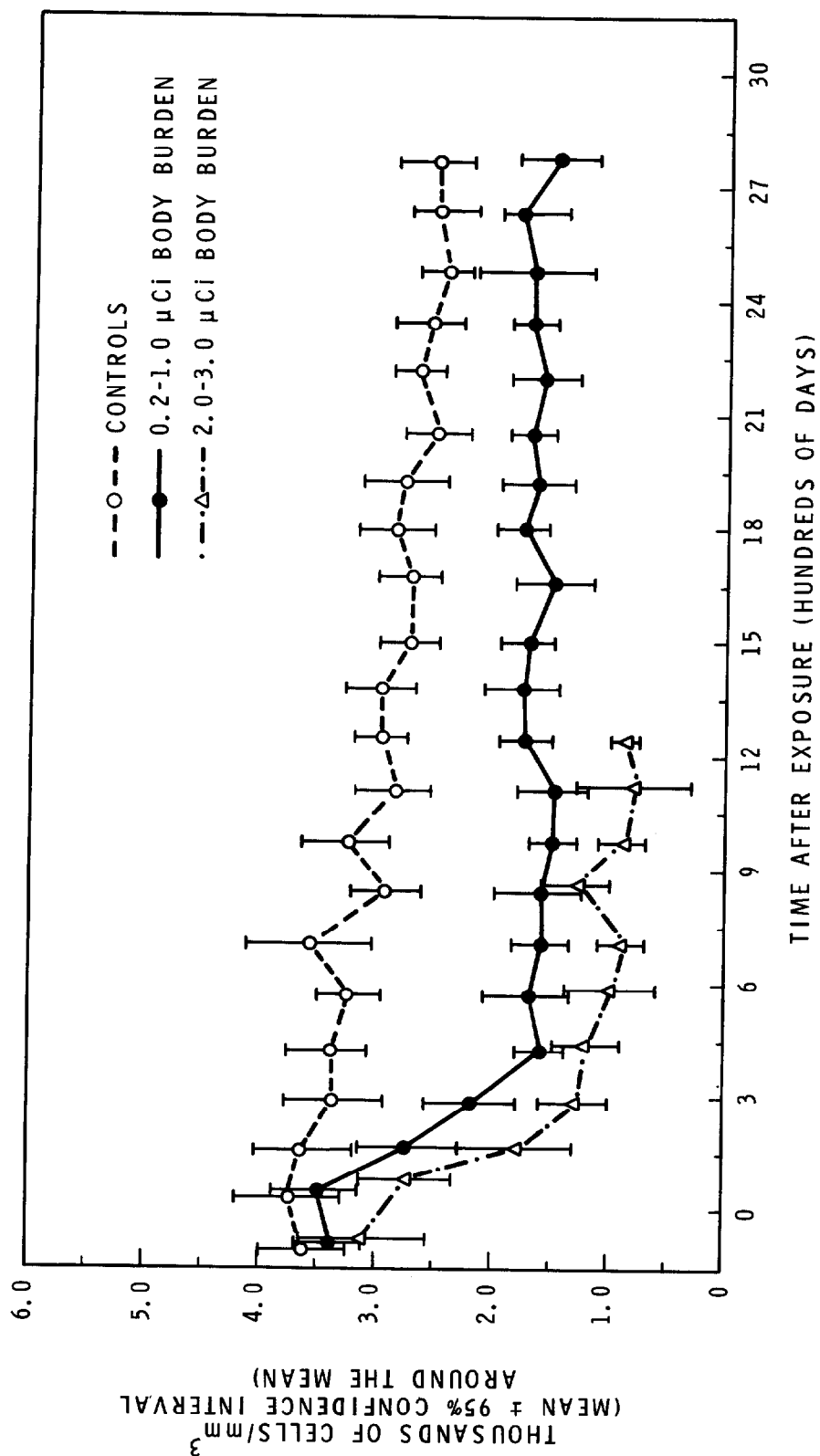***Pharyngeal, Axillary or Mandibular Lymph Nodes

FIGURE 8. Absolute Lymphocyte Values for Dogs after Inhalation of Plutonium (Values given are means for about 10 dogs in each dose group.)

associated decreases in other cellular elements of the circulating blood.

The hematological response to inhaled $^{239}Pu(NO_3)_4$ differed from that for PuO_2. Depending upon the dose, there was a decrease in all leukocytes.

Tests have shown that the lymphopenia is accompanied by a loss of heterophile antibody forming capacity.[14] Other clinical changes are related to the onset of respiratory insufficiency. Respiratory rates tend to increase as the arterial blood pO_2 decreases and the pCO_2 increases.[8]

B. Mortality

Modes of Death

As in the case of most toxic materials, the criterion of greatest interest is the shortening of life span. Depending upon the dose, inhaled plutonium will shorten the life span. The mode of death varies from the acute to the long-term or chronic. Several modes of death have been identified. In the first, deposition of large amounts of plutonium in the lungs can cause death within a week. This acute respiratory death is characterized by severe inflammatory reaction, edema, hemorrhage, and generalized destruction of the functional tissue of the lung. The animal essentially drowns in its own fluids.

The second mode of acute death occurs at somewhat lower doses and at times ranging from about 1 month to several months after exposure. This mode of death differs from the first in that the development of extensive fibrosis is a contributing factor to the loss of functional tissue in the lung. The histopathology is similar to that observed following relatively high doses of X-radiation delivered to the thorax.[15,16] Death is a result of respiratory insufficiency and is preceded by rapidly increasing respiratory rates and by high arterial blood CO_2 and low O_2.

The third mode of death, subacute, is also a respiratory death but occurs at lower plutonium doses. The syndrome is similar to that of the second mode of acute toxicity except that fibrosis develops more gradually and death may occur from 1 year to 3 or 5 years after exposure. In this case the total volume of lung tissue irradiated is much less than in the two acute modes of death, but with time fibrosis initiated at the sites of irradiation may infiltrate progressively the rest of the lung.

Pulmonary neoplasia occurred in many dogs which died a respiratory death 3 to 5 years after exposure.[17] However, neoplasia was the cause of death in a number of animals which survived beyond 5 or 6 years postexposure.[9] Most of these animals showed fibrotic lesions as well, but enough lung tissue remained functional to maintain respiratory requirements.

Although not yet observed, we might speculate upon another mode of death. It is defined as shortening of life by effects of low levels of inhaled plutonium, acting on the lung, tracheobronchial lymph nodes and/or other tissues to which the plutonium is translocated.

Dose Relationship

Sufficient data have been obtained to begin establishment of the quantitative relationship between the amount of plutonium deposited in the lung and shortening of life span. These data provide an opportunity to attempt to extrapolate the results of animal studies to man.

$^{239}PuO_2$
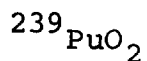
In the earliest experiments we found that dogs depositing more than 0.1 µCi/g of lung died within about a year due to respiratory insufficiency caused by severe irradiation injury of the respiratory tissues.[11] The longer term effects have been studied in 40 dogs which deposited less than 0.1 µCi/g of lung.[9] To date, 10 years after exposure, 30 have died or were sacrificed when death was imminent, and an additional five were sacrificed to obtain tissue distribution data. Twenty-two of the 30 dogs held for duration of life have had primary pulmonary tumors, including all dogs which survived as long as 4-1/2 years postexposure. Of the five dogs still alive, two show radiographic evidence of pulmonary neoplasia.

The lowest lung burdens at death have been about 0.05 µCi. Initial alveolar deposition in these cases is estimated to have been less than 1 µCi.

The lung tumors in all dogs were classified as bronchiolar adenocarcinomas. One dog also had bronchial carcinoma and three dogs, epidermoid carcinomas. One dog also showed a lymphangiosarcoma which appeared to originate in the vicinity of a mediastinal lymph node and two had capillary hemangiomas in the mediastinal lymph nodes. Another dog had a lymphangiosarcoma in the lung and another a capillary hemangioma. One dog also showed lymphoma in the mesenteric and mandibular lymph nodes.

Figure 9 shows the radiographic appearance of these tumors.[18] The thoracic radiograph showed a well demarcated peripherally located tumor in the dorsal part of the right diaphragmatic lobe.

In Figure 10, the survival time of these dogs is plotted as a function of the estimated alveolar deposition.[9] Included are data from relatively acute studies and current data from the long-term experiment. A power function was fitted to the data. One of the two values lower than the other data is for a dog that died of a cardiovascular problem.

From such a plot of the data and extrapolating the curve out to about 15 years, probably the maximum life span of these dogs which were more than 1 year old when exposed, one can estimate the levels of plutonium that will cause life shortening due to pulmonary neoplasia and respiratory insufficiency.
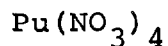
$Pu(NO_3)_4$

The disposition of inhaled $^{239}Pu(NO_3)_4$ was described previously. The lung retained 40 to 70% of the body burden of plutonium as long as 300 days after exposure. These dogs deposited from 6 to 74 µCi of plutonium in their lungs.[6] Mortality occurred from 75 to 303 days after exposure. The cause of death in these dogs was cardiopulmonary insufficiency. Mortality in these dogs is compared to $^{239}PuO_2$ in Figure 11. These data suggest that $^{239}Pu(NO_3)_4$ was as effective as $^{239}PuO_2$ in causing death.

Figure 12 compares the survival times of dogs which inhaled $^{239}Pu(NO_3)_4$ with those which were given plutonium citrate intravenously at the University of Utah.[19] Comparing initial doses of 3 to 4 µCi/kg, the dogs which inhaled $Pu(NO_3)_4$ died after 100 days while those which were given plutonium citrate intravenously survived 1000 to 2000 days--more than 10 times longer than the dogs which inhaled $Pu(NO_3)_4$. Thus, on µCi/kg basis, inhaled $Pu(NO_3)_4$ is acutely more toxic than intravenously injected plutonium citrate.

EXTRAPOLATION TO HUMANS

The objective of these studies is to obtain information that can be used to evaluate the potential risks of human exposures to plutonium. To facilitate the difficult job of extrapolating the disposition data to man, we are developing
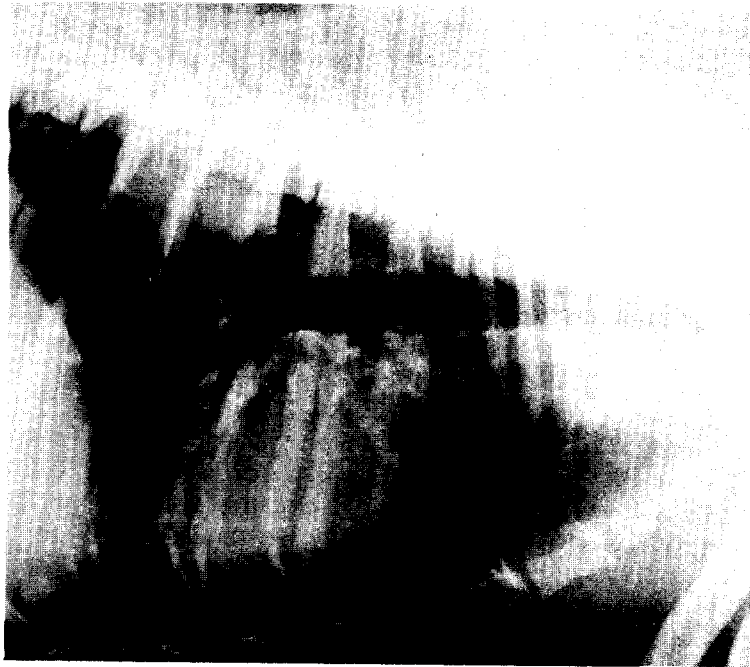
FIGURE 9. Lateral Radiograph of Dog 50
            Months after Inhalation of
            $^{239}PuO_2$. Tumor in Right
            Diaphragmatic Lobe (Lung
            burden $\sim$0.25 µCi)
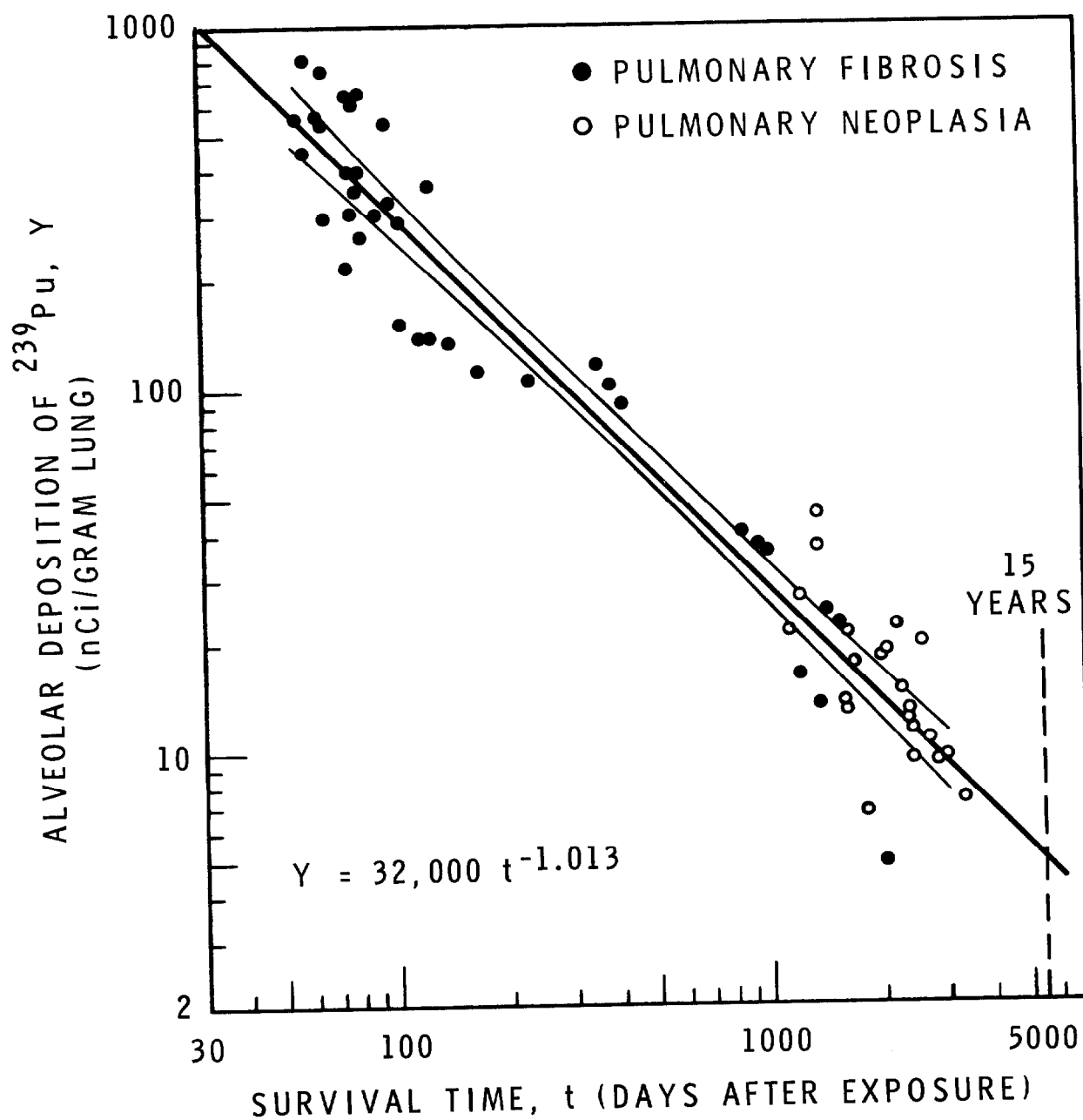
FIGURE 10. Relationship Between Quantity of $^{239}PuO_2$ Deposited and Survival Time of Dogs

FIGURE 11. Survival Time of Beagles after Inhalation of $^{239}Pu(NO_3)_4$ and $^{239}PuO_2$ (6)

FIGURE 12. Survival Time of Beagles after Inhalation of ^{239}Pu Nitrate[6] and Injection of 239Pu Citrate[19]
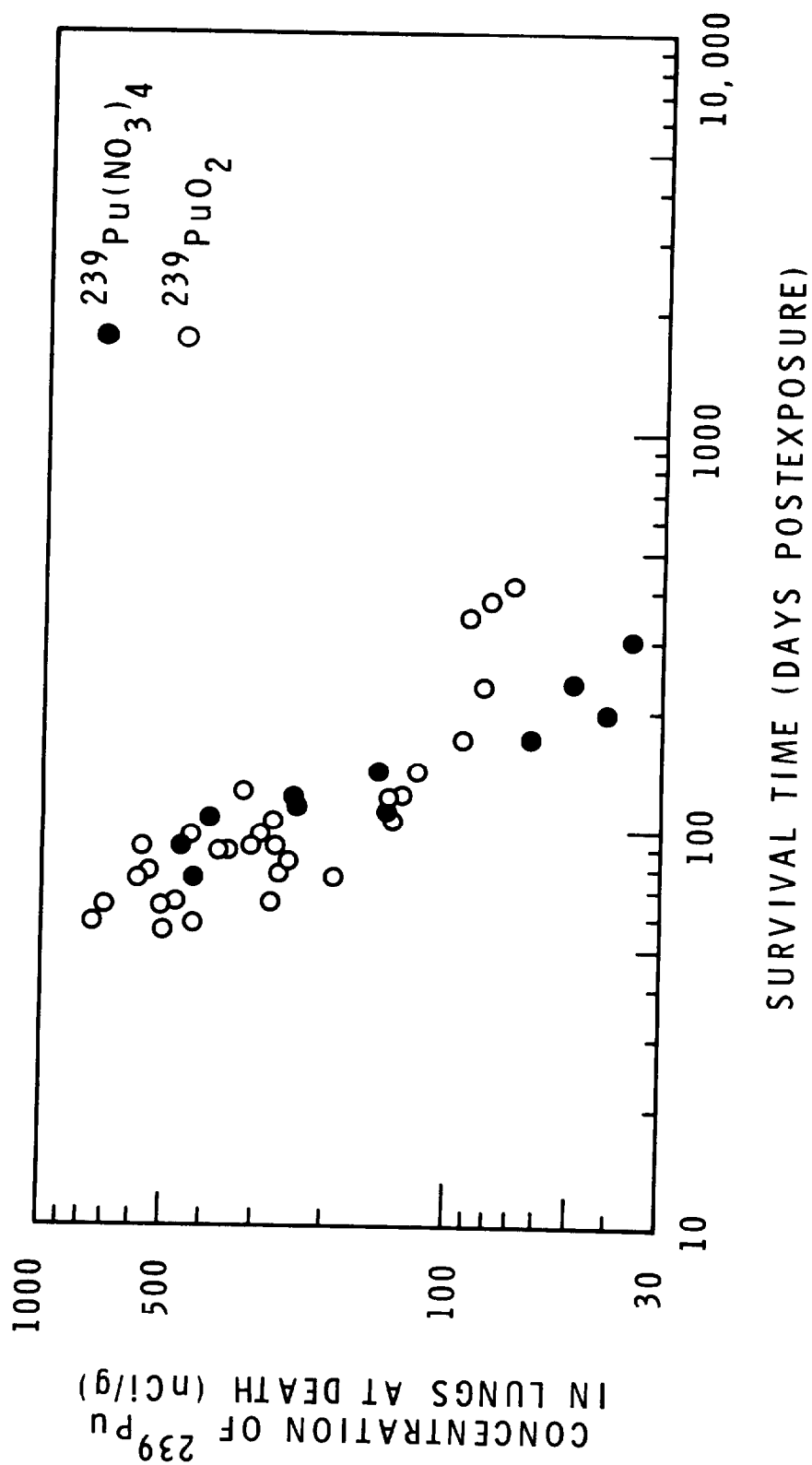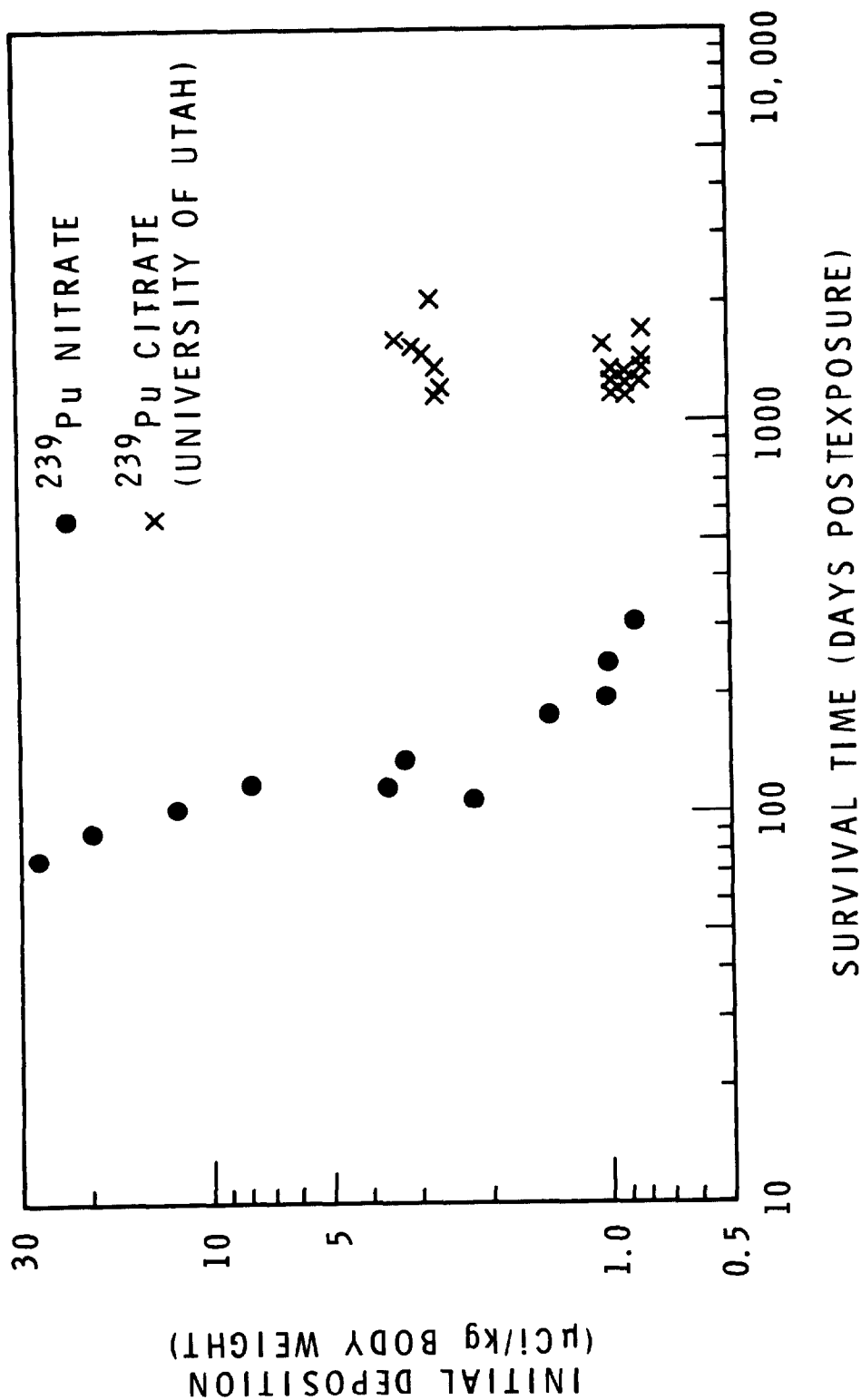
mathematical models. Using data from our long-term dog experiment, a dynamic simulation model for inhaled plutonium dioxide is being constructed with a hybrid computer facility.[20]

This model describes the disposition of plutonium in our dogs which have lived up to about 10 years. If the same compartments and rates apply, this model could be used to predict the disposition of plutonium in man. We hope that data collected by the United States Transuranium Registry and data from other sources can be used to test this model.

A more difficult task is the extrapolation of biological effects data from the animal experiments to man. Two important questions are:

1. Are the tissues of both species equally sensitive to irradiation?

2. How can the latent period for tumor development in an animal species be related to that in the human?

CONCLUSIONS

While we have learned much about the toxicology of inhaled plutonium, much more information is required to assure that it is handled safely. Most of this information must come from animal studies designed for the purpose of extrapolating the results to man. Such studies should not ignore the fact that man's respiratory tract is exposed to numerous substances in the environment and to tobacco smoke and that plutonium may act in concert with some of these substances to cause biological responses.

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A DYNAMIC SIMULATION OF THE RETENTION AND TRANSLOCATION
OF INHALED PLUTONIUM OXIDE IN BEAGLE DOGS*

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ABSTRACT

A dynamic simulation model for the biological disposition of
inhaled plutonium oxide was developed using hybrid computer techniques.
Tissue, blood, and excretion data collected from more than 60 beagle
dogs up to 8 1/2 years after single inhalation exposures to $^{239}PuO_2$
were incorporated into a program that predicts the long-term retention
and translocation of inhaled insoluble plutonium. The dynamic
simulation fitted to the accumulated data shows 10% of the plutonium
initially deposited in the pulmonary lung remains at 12 years after
exposure; the majority of this material follows a 4-year retention
half-time. At 15 to 20 years after exposure the tracheobronchial
lymph nodes, liver, and skeleton burdens plateau at 55%, 16%, and 6%
of the plutonium deposited in the pulmonary lung.

Introduction

The development of simulation models to describe physiological
and biomedical processes has expanded rapidly in recent years. Virtually
any system that involves the interaction of several pools or compartments
according to first-order kinetics can be studied using analog or hybrid
computer techniques, permitting the rapid evaluation of parameter changes
and the prediction of the long-term results on the basis of laboratory
findings. Recently, dynamic simulations have been made of the biological
disposition of radionuclides that may enter the body through several routes
of administration, to determine build-up and elimination patterns of these
materials for radiological dose calculation and subsequent hazard evaluation.
Watson et al. have developed a model for the movement of ingested tellurium –
iodine radioisotopes in large laboratory animals[1], and Bonta has used
similar techniques based on experimental animal data to evaluate the inhalation
hazard of 210-polonium used as thermoelectric generator fuel[2]. In
1966 the Task Group on Lung Dynamics for the International Commission
on Radiological Protection presented a new model for the prediction of
the deposition and retention of inhaled particulate materials, based
upon experimental and computer studies of the deposition of heterogeneous
aerosols and the classification of compounds into general catagories
of minimal, moderate, or avid retention[3]. Dyson and Beach used the
parameters suggested by this model to construct an analog computer simulation

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*This paper is based on work performed under United States Atomic Energy
 Commission Contract AT(45-1)-1830.

of the rates of transfer of inhaled materials of various particle sizes
into the blood[4]. Kotrappa has calculated the theoretical dose to various
regions of the respiratory tract delivered by hypothetical alpha emitters
having varying retention half-times based on the International Commission
on Radiological Protection Task Group lung model[5]. Morrow has recently
suggested that rapid initial clearance of deposited inhaled material
from the upper respiratory tract may be represented in many cases by
a power function, and describes Mercer's solubility model as providing
reasonable agreement with many of the observed clearance rates of specific
compounds from the pulmonary lung[6]. The studies described in this
report were undertaken to provide a dynamic simulation of the biological
disposition of a particularly hazardous alpha-emitting radionuclide, $^{239}PuO_2$.
During a period of 8 1/2 years data have been obtained in our laboratory
on more than sixty beagle dogs after each had inhaled plutonium oxide.
These data on the distribution, excretion, and biological effects of
this material has been used to develop a dynamic simulation of both the
initial and long-term behavior of plutonium dioxide in terms of lung
retention and translocation to other tissues.

METHODS

Beginning in 1960 groups of beagle dogs received single inhalation
exposures to aerosols of calcined $^{239}PuO_2$ having count median diameters
of 0.3 to 0.5 μM. Methods of specific aerosol characterization and exposure
and sampling techniques have been described in detail in several previous
publications[7, 8]. The first step in relating analyzed tissue plutonium
levels to initial deposition is the determination of whole body retention
patterns of the inhaled plutonium oxide. These were obtained by radioanalysis
of all excreta collected from representative animals from time of exposure
to sacrifice. Determination of specific organ and total body plutonium content
plus serial addition of each preceding day's excretion values by computer
produced accurate whole body regression curves with time[9]. Tests of
both multiple exponential and power function fitting to these curves
produced a consistant relationship of the form $Y = A_0t^{-b}$ where A_0 is
the initial (day-one) alveolar burden (a compartment composed of the
functional long-term reservoir of plutonium in the pulmonary lung), Y
is the whole body burden (after the first 10 days postexposure), and
b is a constant with a value of 0.03 ± 0.004. Figure 1 illustrates the
whole body retention curves obtained for representative animals. Individual
tissue levels of plutonium for each animal could then be expressed either
as percent total initial deposition or as percent of initial alveolar
burden.

The retention and translocation model was developed using a hybrid
computer complex consisting of a EASE 2133 analog computer for exact
simultaneous integration of the specified differential equations and
dynamic display, connected to a DEC PDP-7 digital computer for accurate,
high-speed arithmetic computations and data storage[10]. The dynamic
simulation model was set up using the following general form of a linear
first-order differential equation:

$$\left(\frac{dN}{dt}\right)_i = \dot{N}_i = f_{i,j}(\lambda_{b,j})N_j - (\lambda_{e,i})N_i$$
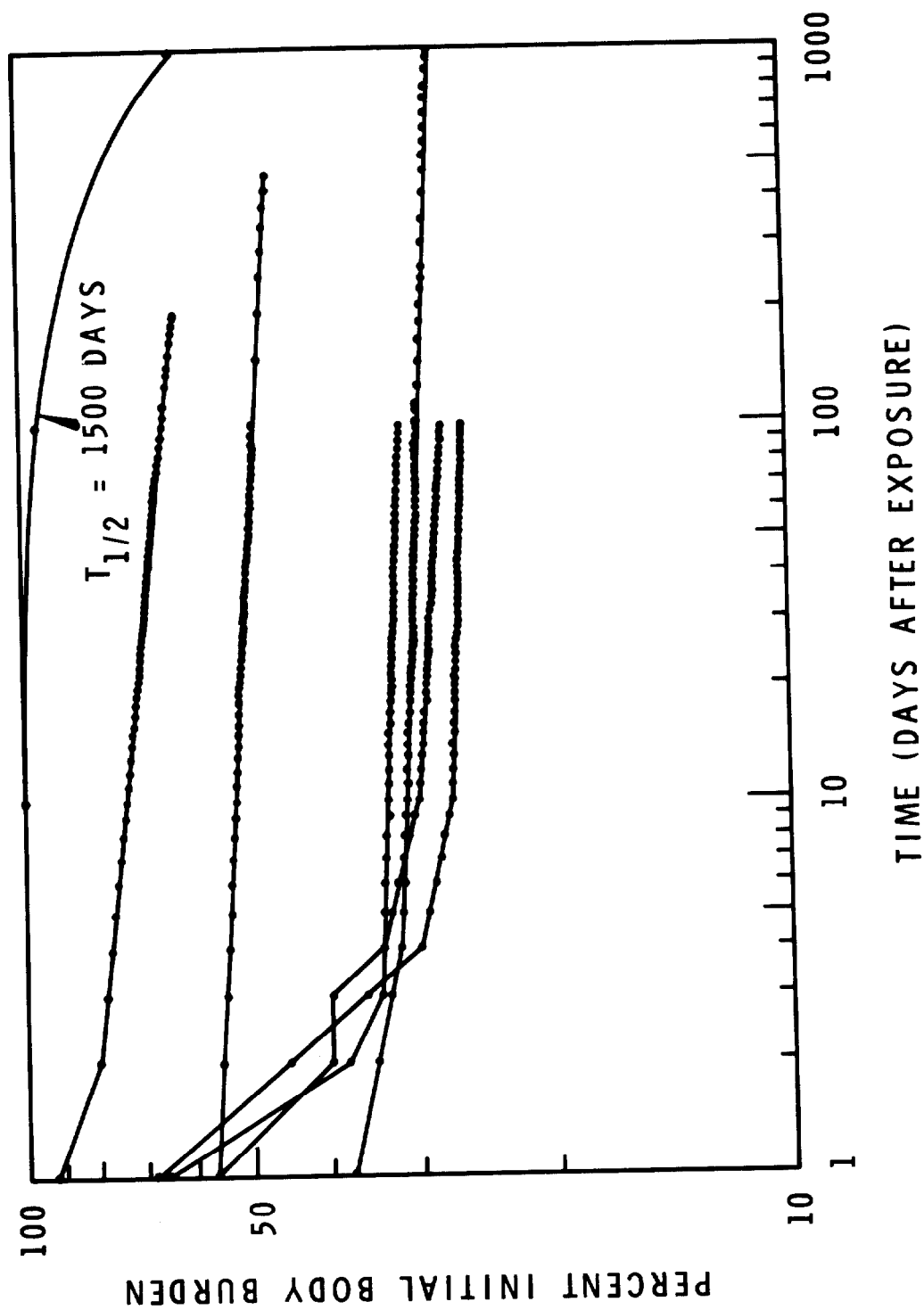
FIGURE 1. WHOLE BODY RETENTION OF PLUTONIUM IN BEAGLE DOGS AFTER INHALATION OF $^{239}PuO_2$

Here $\left(\frac{dN}{dt}\right)_i$ is the time rate of change of burden in the <u>i</u>th organ,

$f_{i,j}$ is the fractional uptake by the <u>i</u>th organ from the <u>j</u>th organ,

$\lambda_{b,j}$ is the biological rate of elimination from the <u>j</u>th organ, and

$\lambda_{e,i}$ is the effective rate of elimination from the <u>i</u>th organ. For the case of 239-plutonium, having a physical half-life of 24,360 years, $\lambda_{e,i} = \lambda_{b,i}$.

Two hybrid computer simulations of the inhalation model have been developed. A short-term model was developed to describe the initial deep lung (pulmonary) deposition and early systemic organ burdens, given early fecal and whole body retention data. Given the initial deep lung deposition (A_0, as determined from the whole body retention curve) the long-term model predicts the organ burdens fifteen or more years after exposure.

The fractional uptake constants and the biological elimination rates for each compartment were obtained by fitting the model to the data by minimizing the integral of a normal error squared function to the build-up curve for each organ and for the total body[11]. This function is expressed as:

$$E_i = \int_0^t \left(\frac{data_i - model_i}{model_i}\right)^2 dt.$$

The hybrid computer oscilloscope display can be used for immediate visualization of the "goodness-of-fit" of any desired model change to the stored data points.

Figure 2 illustrates typical simultaneous visual displays of data points (interconnected by straight-time segments), fitted simulation curves, and associated integral error squared functions for the pulmonary lung and tracheobronchial plus mediastinal lymph node compartments. Rapid evaluations of proposed changes in compartment structure, fractions, and half-times are possible using this technique.

RESULTS AND DISCUSSION

The short-term dynamic simulation of the disposition of inhaled plutonium oxide contains eleven compartments is shown in Figure 3. The initial lung deposition of $^{239}PuO_2$ is split among two compartments; a combined nasopharynx-tracheobronchial compartment having an effective removal half-time of eight minutes (the Task Group on Lung Dynamics suggests 4 and 10 min half-times for rapid clearance pathways[3]) and a pulmonary compartment with an effective plutonium elimination rate long enough so that essentially none leaves during the first seven days. The deposition percentages are 70% in the nasopharynx-tracheobronchial compartment and 30% in the pulmonary compartment, relative to the total amount deposited. The arrows in Figure 3 indicate the important pathways by which the material leaves the lung. The biological half-times shown in the parentheses in the various compartments are taken from the ICRP Task Group II lung model[3] and I.S. Eve's values for the GI tract[12]. The soluble portion ($\approx 0.3\%$) of the amount deposited in the nasopharynx-tracheobronchial

PULMONARY LUNG BURDENS

PERCENT ALVEOLAR DEPOSITION

- ERROR SQUARED FUNCTION
- SIMULATION MODEL
- INTERCONNECTED DATA POINTS

YEARS AFTER EXPOSURE

TRACHEOBRONCHIAL AND MEDIASTINAL LYMPH NODE BURDENS

PERCENT ALVEOLAR DEPOSITION

- SIMULATION MODEL
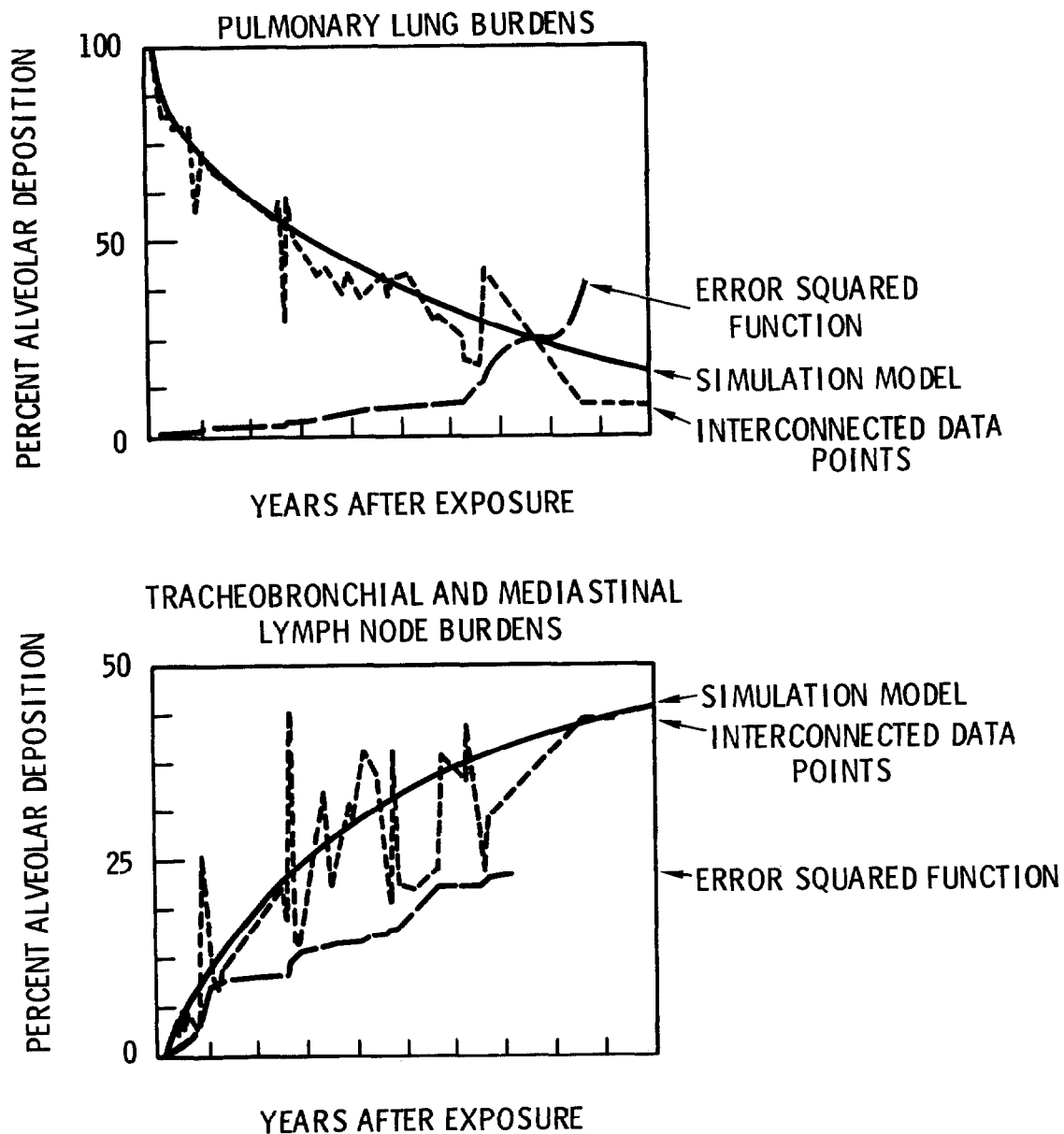- INTERCONNECTED DATA POINTS
- ERROR SQUARED FUNCTION

YEARS AFTER EXPOSURE

FIGURE 2. TYPICAL OSCILLOSCOPE TRACINGS OF THE DATA, DYNAMIC
SIMULATIONS, AND ERROR SQUARED FUNCTIONS USING
HYBRID COMPUTER TECHNIQUES.

70% OF TOTAL DEPOSITED

NASOPHARYNX-
TRACHEOBRON-
CHIAL (8 MINUTES)

99.7%

0.3%

BLOOD
(8 HOURS)

30% OF TOTAL DEPOSITED*

STOMACH
(1 HOUR TRANSIT)

100%

SMALL INTESTINE
(4 HOURS TRANSIT)

100%

UPPER LARGE
INTESTINE
(13 HOURS TRANSIT)

100%

LOWER LARGE
INTESTINE
(24 HOURS TRANSIT)

PULMONARY
LUNG

SKELETON

25%

KIDNEYS

2%

URINE

2%

LIVER

71%
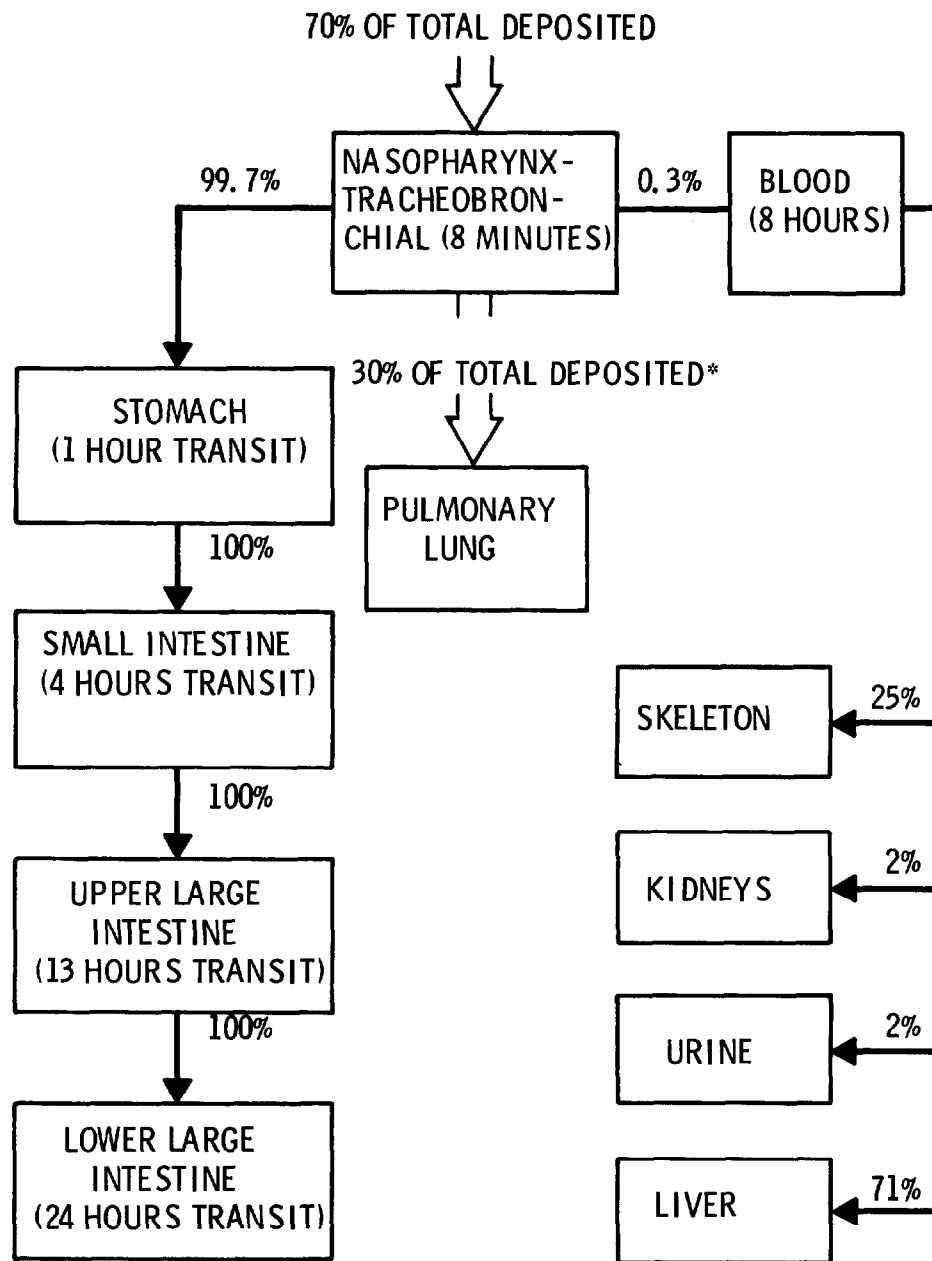
* INITIAL ALVEOLAR DEPOSITION

FIGURE 3. BLOCK DIAGRAM OF THE SHORT-TERM DYNAMIC SIMULATION
OF THE DEPOSITION AND RAPID CLEARANCE OF INHALED
$^{239}PuO_2$

compartment enters the blood, and the remainder enters the gastrointestinal tract by ciliary-mucus transport. Figure 4 shows the build-up and elimination of plutonium in the nasopharynx-tracheobronchial, blood, and gastrointestinal compartments during the first week after exposure. During this time the compartments with short biological half-times have nearly eliminated their burdens. The peak levels in the GI tract compartments are 32-45% of the total plutonium initally deposited; the blood level peaks at ≃ 0.2% and drops to very low levels after the second day.

Our studies with beagle dogs show a high degree of variability in the percentage of initial total deposition which is found in the nasopharynx and tracheobronchial regions of the respiratory tract, ranging from 20% to 80%[7, 8, 9, 13]. After the initial rapid clearance of insoluble plutonium from the nasopharynx-tracheobronchial compartment via the gastrointestinal tract, the long-term total body burden of inhaled plutonium will depend primarily upon the rates of clearance from the pulmonary lung to the lymph nodes, skeleton, liver, and kidneys. The last three will have small initial burdens from the 0.3% initially soluble component of the dust deposited in the respiratory tract which passes rapidly into the blood and on to the systemic organs. However these initial contributions provide at most only 3% to 8% of the total long-term burdens that gradually build up in the skeleton, liver, and kidneys from slow pulmonary clearance. Thus, changes in these low initial contributions caused by changing initial nasopharynx-tracheobronchial deposition from 80% to 20% have negligible effect upon the total long-term levels of these organs. Because of these findings, it was decided to base the long-term model on the initial levels of plutonium deposited in the slow pulmonary compartment, assuming that plutonium dioxide had a very low solubility (< 1%) in lung fluids.

Figure 5 shows the long-term dynamic simulation model that was developed to describe the translocation and excretion of plutonium deposited in the slow pulmonary compartment. This reservoir of avidly retained plutonium is split into two portions. The major component of this material (85%) is gradually translocated to the tracheobronchial and mediastinal lymph nodes with a four-year half-time. About one-tenth (9%) of this material is removed to the tracheobronchial lymph nodes, nine-tenths is transported to the GI tract, and a small amount (1%) enters the blood. The remaining 15% of pulmonary deposited plutonium has a variable elimination rate, being 50 days initially and doubling every year. Testing of the tracheobronchial and mediastinal lymph node clearance by minimizing the integral error squared function for best fit and by observing resultant changes in whole body and systemic organ curves showed that only 30% of the lymph node burden seemed to be available for transfer to the blood. A one year clearance half-time for this transfer gave the best fit to the observed radioanalytical data of tissue plutonium levels. The same methods of testing showed the fractions of plutonium that leave the blood and enter the systemic organs to be 70%, 25%, and 2% for the liver, skeleton, and kidneys respectively. These values for liver and skeletal fractions are nearly the reverse of the corresponding fractions suggested by the ICRP[14] based primarily on data from small animals injected with relatively soluble plutonium.
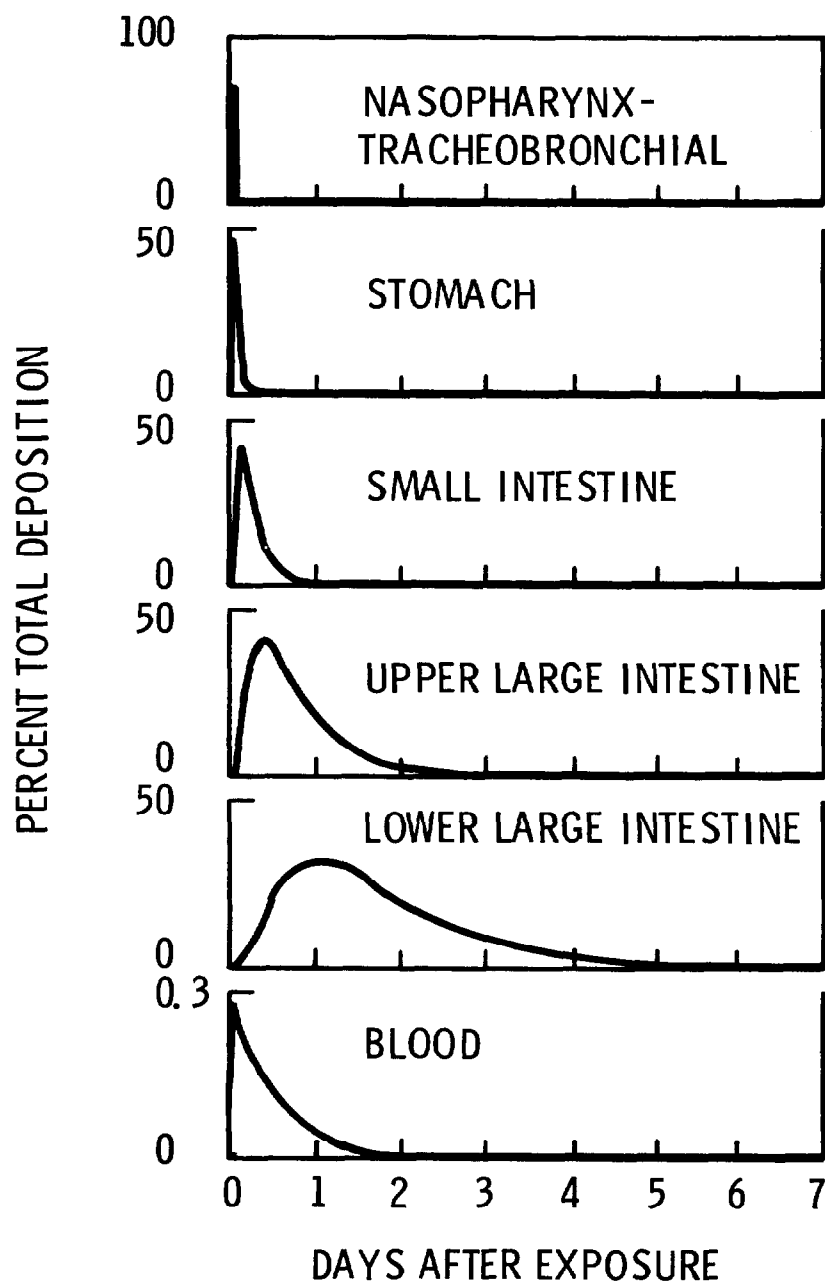
FIGURE 4. RESULTS OF THE SHORT-TERM MODEL FOR INHALED
PLUTONIUM OXIDE
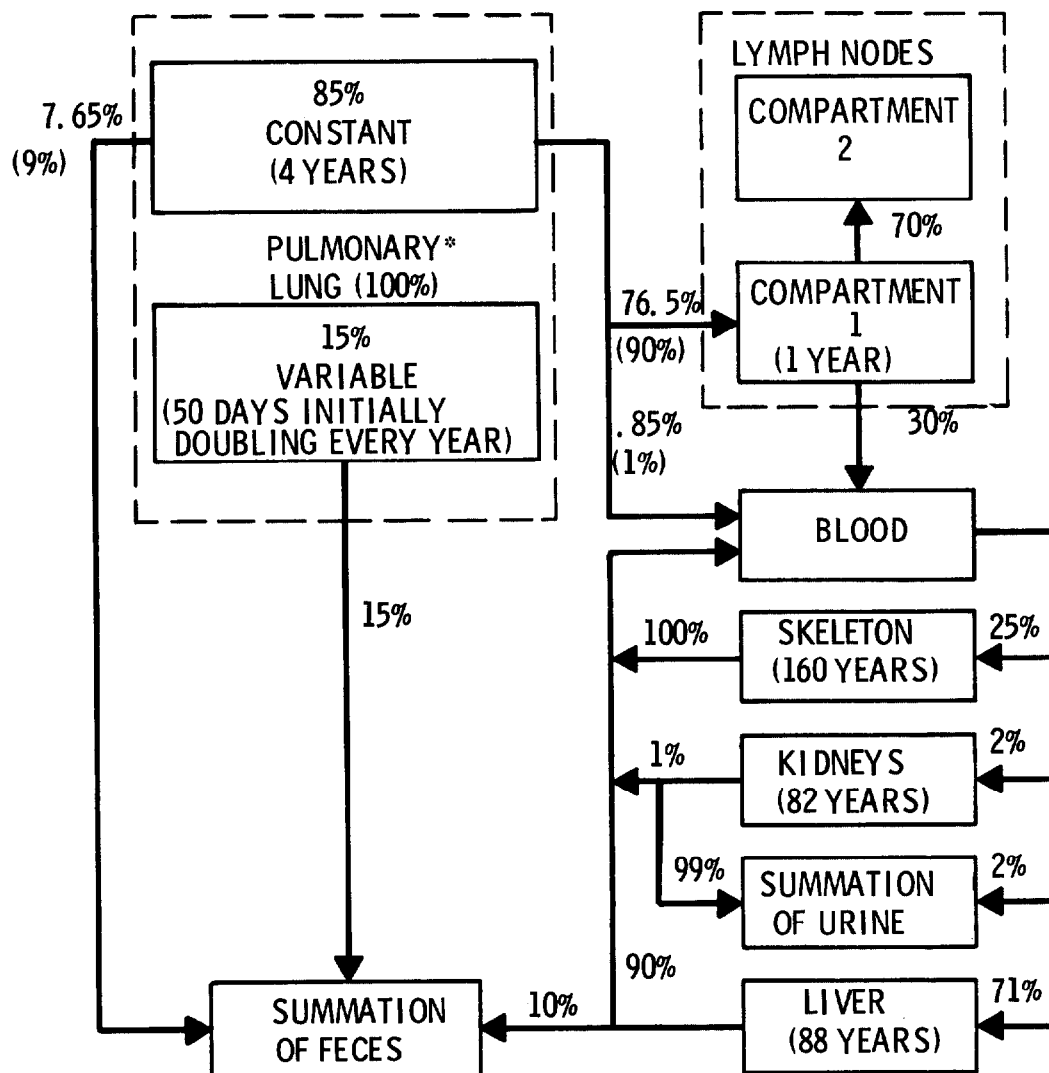
* BASED ON 100% OF THE INITIAL ALVEOLAR DEPOSITION.

FIGURE 5.   BLOCK DIAGRAM OF THE LONG-TERM DYNAMIC SIMULATION
OF THE PULMONARY RETENTION AND TRANSLOCATION OF
INHALED $^{239}PuO_2$

FIGURE 6.   RESULTS OF THE LONG-TERM MODEL FOR INHALED
             PLUTONIUM OXIDE, BASED ON THE INITIAL ALVEOLAR
             DEPOSITION.   DATA FOR THE PULMONARY LUNG,
             TRACHEOBRONCHIAL LYMPH NODES, SKELETON AND LIVER
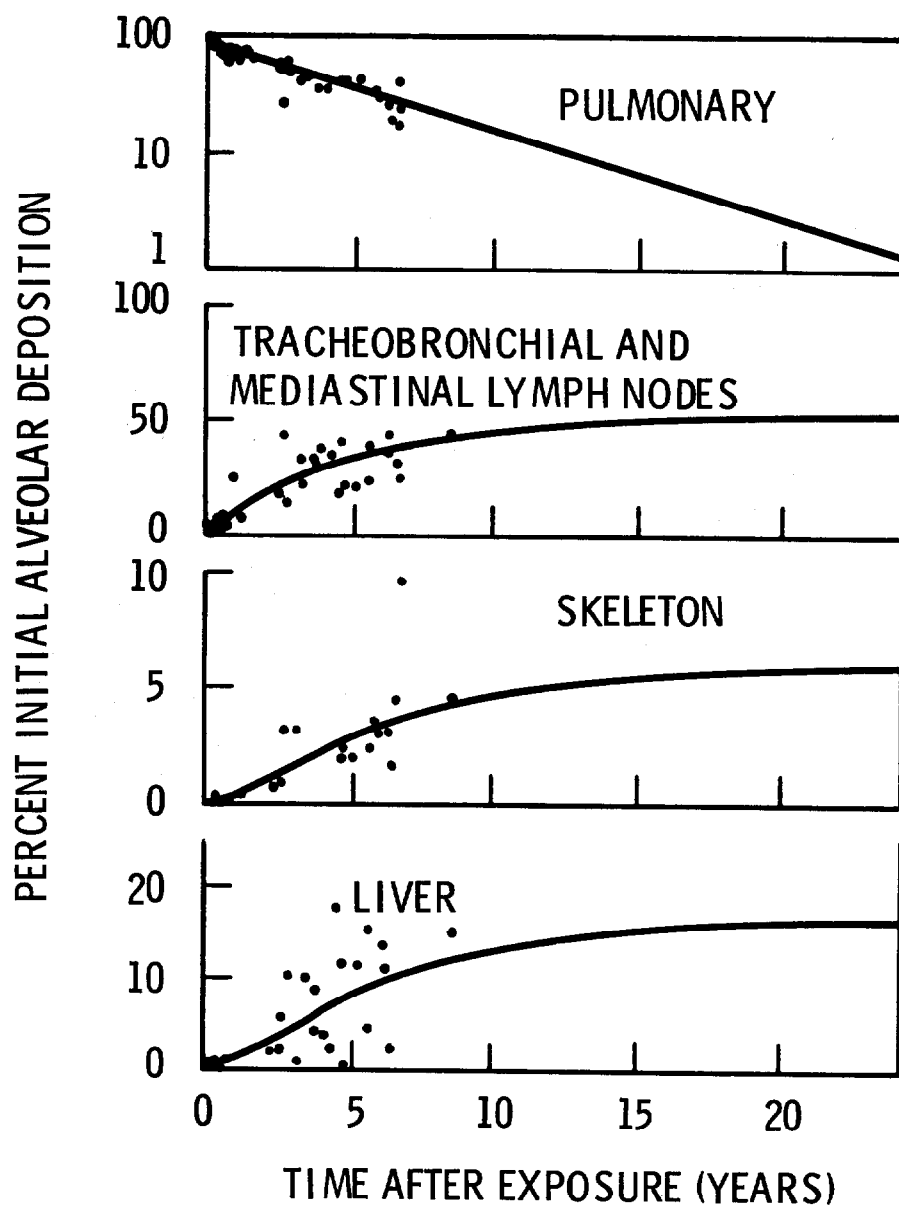   ARE INCLUDED.
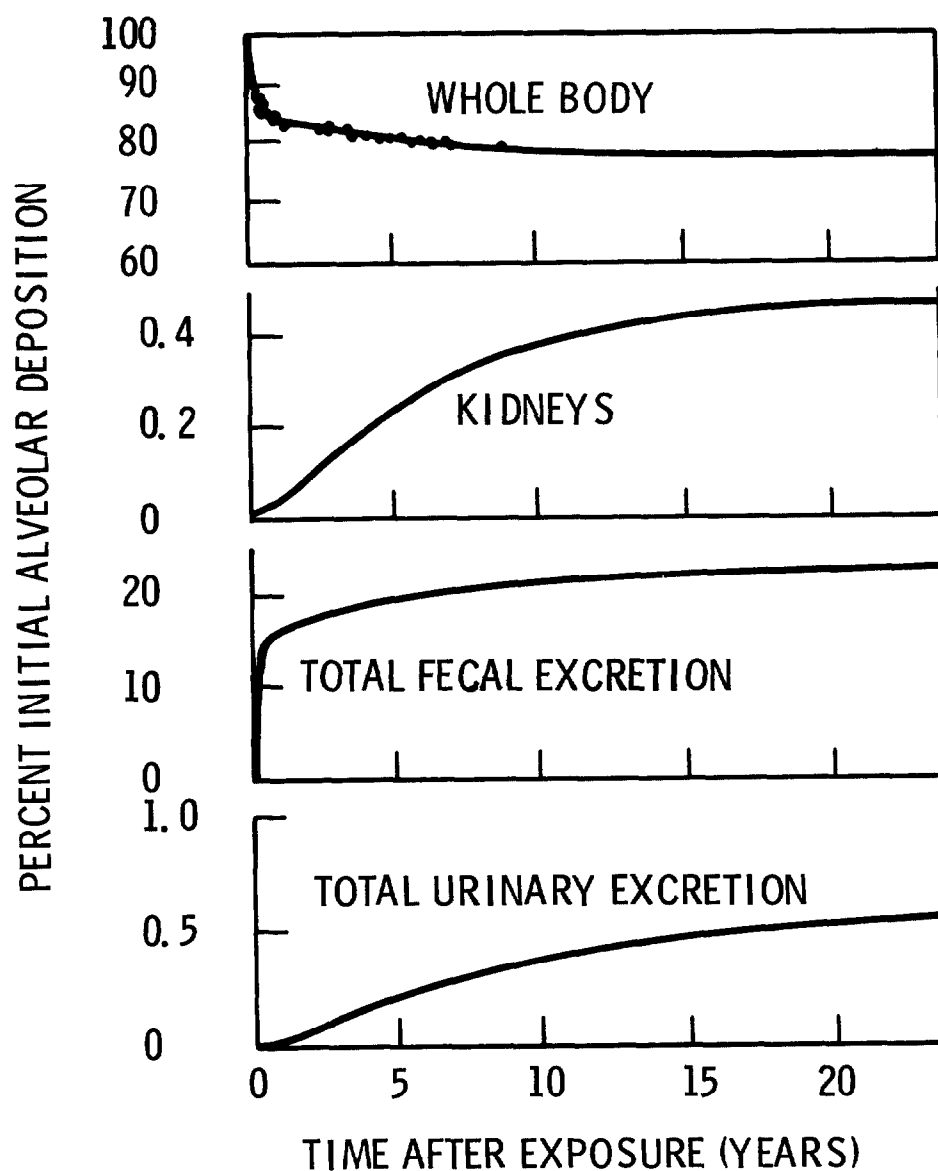
FIGURE 7.   RESULTS OF THE LONG-TERM MODEL FOR INHALED
            PLUTONIUM OXIDE, BASED ON THE INITIAL ALVEOLAR
            DEPOSITION.   FITTED CURVES FOR WHOLE BODY,
            KIDNEYS, AND CUMMULATIVE EXCRETION LEVELS ARE SHOWN.

Figures 6 and 7 show the long-term pulmonary retentions, systemic organ accumulations and accumulative excretion levels of plutonium deposited initially in the pulmonary or alveolar lung. The whole body and specific tissue data points to which the long-term dynamic simulation was modeled are included. Pulmonary and whole body curves are plotted with exponentially-scaled ordinates. The plutonium burden in the dog lung decays to about 10% of the initially deposited amount in twelve years. Tracheobronchial and mediastinal lymph node burdens continue to rise and apparently do not plateau until after twenty years. Liver, skeletal, and kidney burdens all start with very small initial inputs from the 0.3% initially soluble fraction of plutonium deposited in the lungs that reaches the blood within one or two days after exposure. Plutonium build-up in the liver reaches a peak level of about 16%; corresponding levels in the skeleton and kidneys are about 6% and 0.5% respectively.

Conclusions

Radioanalytical data from tissues, blood, and excreta samples collected from over sixty dogs up to 8 1/2 years after exposure have been used to develope a dynamic simulation of the long-term disposition of inhaled plutonium oxide in beagle dogs. After the model has been accurately fitted to measured values, it can be used to predict long-term tissue burdens for calculation of radiological dose rates and cummulative dose. This information can then be used to identify possible critical organs for inhaled plutonium dioxide. Information gained from the dynamic simulation model can also be used to define further research requirements, and to help plan future experiments.

The model based on available data from continuing experiments of inhaled plutonium oxide suggest a four-year half-time for clearance of 85% of the material deposited as an initial alveolar burden, with translocation predominantly to the tracheobronchial and mediastinal lymph nodes. A large fraction (70%) of the plutonium reaching these nodes seems to be retained indefinitely; the remaining 30% may be transported to blood, with a one-year half-time. Although studies of injected relatively soluble plutonium in beagle dogs suggest half-times on the order of 5-10 years for systemic organs[15, 16], liver and skeletal translocation patterns of inhaled insoluble plutonium in our studies were better fitted using 82 and 160 year half-times, similar to those recommended by the International Commission on Radiological Protection[14].

This dynamic simulation model for inhaled PuO_2 in dogs was developed from data obtained from dogs given a single exposure to a PuO_2 aerosol having rather specific physical and chemical characteristics. Additional work is required to determine how well the model applies to PuO_2 aerosols of different characteristics. This model based on single inhalation exposures can be used directly to construct a dynamic simulation of the long-term retention and translocation of plutonium oxide deposited during chronic or multiple-inhalation exposures. However the validity of the chronic inhalation exposure model should be tested experimentally.

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DISCUSSION

HONSTEAD: I have a question on the last point that you made concerning the concentration of plutonium in the liver. Did you find any cancers occurring in the liver that might correlate with the plutonium deposition?

STUART: The lung tumors were bronchiolo-alveolar carcinomas. One dog also showed a lymphangiosarcoma, arising near a mediastinal lymph node. No tumors have been found in the skeleton, liver, or kidneys.

SCHINDLER: Could you tell what the physical form of the plutonium found in the lymph nodes was?

BAIR: It's primarily particulate. However, single tracks are occasionally seen in autoradiograms of tissue sections. These may originate from ionic plutonium, but more likely they originate from small particles.

MERZ: A question of Dr. Bair. In your concluding remarks you commented on the difficulty in extrapolating the animal test data to humans and you summarized it in the form of several questions that need to be answered, for instance, relative sensitivity of the tissues. Could you comment on how and when and if these questions can be answered?

BAIR: I wish I could. I think eventually we will have a better understanding of some of these processes. As a result of the type of experiments we are trying to do we should become more intelligent in extrapolating the results of animal experiments to man. This extrapolation is very difficult because comparative experiments with human subjects are not possible. We have to rely on data obtained on several animal species to provide a basis for predicting the response of human tissue to a particular agent. Occasionally, we have the benefit of data obtained from an accidental exposure of humans to the agent of interest.

JOHNSTON: Are you finding any isotopic effects when you are dealing with ^{238}Pu?

STUART: This is an involved question. In both rats and dogs the acute effects are similar. Rats that received initial alveolar depositions of up to 50 μCi of either ^{239}PuO$_2$ or ^{238}PuO$_2$ died within a week due to flooding of the lungs with proteinaceous fluid. Both isotopes produced some degree of fibrosis and alveolar cell proliferation. The question

that must be resolved is the comparative long-term toxicity of each of these isotopes. The long-term effects of much lower lung burdens of these radionuclides are being studied in our laboratory using beagle dogs.

DAVIS: Plutonium is deposited in the lung and then it seems to take a considerable length of time to move to other organs. This suggests, I suppose, that one might intercept it on its way and somehow devise remedial measures on this basis. I wonder if you have thought about that kind of thing, or is that kind of thing a long way off?

STUART: Dr. Dilley of our laboratory has studied the possible removal of inhaled plutonium using a variety of agents. Among the most promising therapeutic compounds that have been tested are phenolthiazine derivatives and some steroids.

BLAIR: Dr. Sanders, who is in the audience, has been studying the effectiveness of removing plutonium from the lungs by lavage -- washing the lung with a saline solution. This is perhaps a useful technique. Dr. Dilley in our laboratory is testing a number of pharmaceutical agents for removing inhaled plutonium. We are interested in developing a method for removing all the plutonium including that translocated to the lymph nodes. However, it may be fortuitous that this material is accumulating in the lymph nodes and, if that is the case, we shouldn't do anything about it. Some of these questions are certainly pertinent before one goes very far in trying to intercept this material in a human exposure case, such as by the use of surgical techniques to remove lymph nodes that have accumulated plutonium.

CRAIG: This is perhaps not a very fair question, and it is for Dr. Stuart. Much of the data upon which your modeling is done is based upon experiments that were carried out with plutonium dioxide formed from the oxylate by calcining it at 350°C. Now my investigations in the past few weeks have indicated that this material may contain quite a lot of residual carbon, some chlorides and some fluorides. I wonder if you would care to speculate as to how much this might have affected the sort of distribution or redistribution of materials that you see to tissues other than the lymph nodes?

STUART: In our previous conversations, the figures discussed were 600-700 parts per million of carbon. In the present studies we have on the order of 1 microcurie initial alveolar deposition, or about 17 micrograms of plutonium. To be perfectly honest, I don't know whether this carbon impurity may affect translocation to systemic organs. Dr. Bair has found some changes in the biological disposition of several plutonium oxides calcined at different temperatures. The material that was studied in the experiments described here was calcined at 350°C and was felt to be typical of that plutonium oxide which may be released during accidental burn situations.

BAIR: This is an important point because in our studies
we are attempting to provide information useful to the nuclear industry.
When our long term study began over ten years ago, the material we used
was that which was most commonly encountered in the plutonium industry.
Of course plutonium technology has changed. One of our current problems
is to determine the material we should use in new experiments that will be
concluded fifteen years from now so that results obtained then will be useful
at that time. Thus, we have to depend upon reactor physicists to keep us
informed of future trends in the technology and possible health problems.

THAXTER: Is it too early to give a ball park figure for the
initiation of disease or should I say carcinogenesis in the dog, in the
sensitive tissues that you have observed, in terms of total rem absorbed
dose?

BAIR: The average accumulative dose to the total lung
in most of these cases was 2000 to 5000 rads. This value doesn't mean
very much because the plutonium dioxide is not uniformly distributed
throughout the lung, but is concentrated in hot spots. I pointed out with
one slide how cells are able to concentrate plutonium particles. Certainly
localized areas within the lungs are exposed to radiation doses far exceeding
5000 rads. We don't know the radiation dose that actually caused the neo-
plastic changes in our dogs.

STUART: I think personally, that this is one of the most
difficult problems in the field today, because these are discrete hot-spot
particles. One can analyze the total amount of plutonium in the lung at
death or sacrifice, average that over the weight of the lung and arrive at
a figure. But the microscopic dose distribution is extremely complex,
and very difficult to relate to the overall probability of cancer production.

KOONTZ: Has your data effectively changed the presently
accepted body burden for humans? Would you say that we should use the
same values, increase them or decrease them?

BAIR: We are not prepared to make any recommendations
at this point. I don't know whether any of our results to date have resulted
in any major changes in the permissible limits but our results apparently
have been useful to those bodies concerned with establishing limits.